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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,372	03/03/2005	IWAO OHIZUMI	1254-0274PUS1	3366

2292 7590 03/15/2010

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
03/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/526,372	OHIZUMI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-2, 5-7, 9, 13-18, 21-22, 24 and 26* is/are pending in the application.

4a) Of the above claim(s) *15,17,22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,13,14,16,18,21 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/25/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/17/2010 has been entered.

2. Claims 1-2, 5-7, 9, 13-18, 21-22, 24 and 26 are pending.

3. Claims 15, 17, 22 and 24 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26 are under consideration in the instant application.

5. The Tomer et al., reference and US Pat. No. 4,942,131 listed on PTO-892 are provided by Applicant, and will not be supplied.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 7, 9, 14, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase “human native protein” claimed in claim 7, represents a departure from the specification and the claims as originally filed.

Applicant’s amendments filed 01/29/2008 and 02/17/2010 points to the specification at page 5, lines 10-11, and pages 8-10, and by the knowledge of one of ordinary skill in the art, who knows and understanding what is generally meant by the term "homology" for support for the newly added limitation “human native protein” as claimed in claim 7. However, the specification does not provide a clear support of “human native protein”. The word “native” is not part of the specification. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

7. Claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing antibody against GPC-3 protein comprising immunizing MLR/lpr mouse that develops SLE with a GPC-3 protein, does not reasonably provide enablement for methods recited in claims 1-9, 1314, 16, 18-21, 23 and 25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

At issue is the term "Fas function defects" which reads on any gene knock out that affect the function of Fas. Besides Fas ligand defects and mutated Fas gene, the specification fails to disclose what upstream or downstream genes that would lead to "Fas function defects". The resulting genotype and phenotype of the nonhuman animal that develops autoimmune disease including Fas function defects vary significantly depending on the genes being manipulated, and the animals being used because gene manipulation and the resulting phenotype of transgenic animals is not always consistent due to reasons such as gene functional redundancy and species difference, and that homozygous transgenic animal may not be viable. Pearson (Nature 2002;415:8-9) comments, " Indeed, clear and consistent phenotypes now seem to be the exception rather than the rule. " (left column, page 8). Accordingly, the phenotypes resulting from homozygous knock out of a particular antigen are expected to be varied and unpredictable. The skilled artisan could not practice the invention without first carrying out undue experimentation to make a homozygous knockout for any particular gene encoding an auto-antigen.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for producing antibody against GPC-3 protein comprising immunizing MLR/lpr mouse that develops SLE with a GPC-3 protein.

Applicant is not in possession of the methods recited in claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (Fas function defects) to describe the claimed genus, nor does it provide a description of structural features that are common to species (Fas function defects). The specification provides no structural description of Fas function defects other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed Fas function defects looks like. The specification's disclosure is inadequate to describe the claimed genus of Fas function defects.

Applicant has discloses only two species of Fas function defects; therefore, the skilled artisan cannot envision all the contemplated Fas function defects possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 7, 9, 14, 16 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Pat. No. 6,235,714.

The `714 patent teaches six MRL/lpr mice were hyperimmunized with target antigen such as EGFR, TNFα, IL-1β among others (see fig. 19 and col., 8, under selection and preparation of CRAAs in particular) to drive the immune system to generate catalytic antibodies. Blood will be obtained from the retro-orbital plexus at ten day intervals (see col., 14, under immunization, col., 43, lines 56-66 in particular). . The `714 patent teaches that target antigens listed in Fig. 19 such as Macrophage inhibitory factor (MIF), C5, GPIIb/IIIa receptor (96% at the amino acid level), FVII, IL-4, IL-5, IgE, Eotaxin, PDGF, αvβ3 integrin (96% at the amino acid level).The target antigen proteins listed in fig. 19 exhibit human native proteins which have an amino acid sequence homology 94 % or higher in the absence of evidence to the contrary. The `714 patent further teaches that the MRL/lpr mouse strain, contain a mutation of the Fas apoptosis gene is believed to permit proliferation of T and B cells and expression of lupus-like disease (see col. 36, lines 63-65). The `714 patent teaches that the human antigen in the exemplary CRAA-IL1-β peptide (PKKKMEK) (see fig. 16) shares a native protein which has PKKKMEK sequence identity of 100% at the amino acid sequence level to the mouse protein antigen (see Exhibit A, under amino acid positions in the "Query" 90-97 provided in the previous Office Actions).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 02/17/2010, have been fully considered, but have not been found convincing.

Applicant submits that the reject states that Paul teaches that the human antigen in the exemplary CRAA-IL1-b peptide, (PKKKMEK) has 100% identity at the amino acid sequence level to the mouse protein antigen. Applicant submits that the antigens described in Paul are not encompassed by the human native proteins described in independent claim 7. As Applicants noted previously, the claims specify native proteins and native proteins do not encompass the PKKKMEK sequence. In addition, independent claim 7, as amended, does not encompass the antigen fragments as allegedly described in Paul, since the claims describe "a human native protein which has a sequence identity of 94% or more at the amino acid level to a homolog protein over the whole length of the mouse to be immunized."

However, enablement does not require that the disclosure in a document establish an actual reduction to practice for it to be enabling. In re Donhue II, 226 USPQ 619 Fed. Cir. 1985). A constructive reduction to practice constitutes an anticipation. In the instant case, the claims are

directed to a process for producing an antibody by immunizing Fas function defects with a human native proteins, the `714 patent teaches the same method of making an antibody using the same mice and the same antigen.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-01047390 (IDS ref. No. BB) OR US. Pat. No. 4,965,198 (IDS AA), each in view of Makino et al (J Clin Lab Immunol. 1988 Feb;25(2):83-8) and Lage et al (2001, IDS CA).

The `390 publication teaches that a mouse having an autoimmune disease such as MRL/I mouse can be used to produce a monoclonal antibody (see the English translation provided by Applicant). The `390 publication teaches a method of producing a hybridoma which produces the monoclonal antibody, wherein an animal having an autoimmune disease is used as a mammal from which plasma cells are obtained. It is preferable that the animal is selected considering the adaptability to myeloma used for cell fusion. A mouse or rat is preferable, wherein the mouse having an autoimmune disease includes N2B, NZW, B/WF1, MRL/I, BXSB male and SLN1 strain. A rat having an autoimmune disease includes a rat in which hypertension occurs spontaneously. Further, a normal mouse such as Balb/c of which the ability to produce autoantibodies increases by being administered with a polyclonal B cells activator such as lipopolysaccharide (LPS) of a gram negative bacterium and dextran sulfate and which is in the state of autoimmune disease may be used (see the Partial English translation of Japanese Publication No. 0104739).

The `198 patent teaches a preparation containing immunogens is used to immunize animals. Thereupon, the immunized animals are preferred to be selected with consideration of their compatibility with the myeloma used in cell fusion. Mice or rats are preferable. When using glycolipids which contain N-glycolylneuraminic acid, an object of this invention, animals with autoimmune disease are more preferable and mice with autoimmune disease are the most preferable. As the mice with autoimmune disease, there are NZB, NZW, B/WF1, MRL/l, BXSB (SLE) male, SL/Ni and other mice available. Normal mice such as Balb/c may be used as

immunized animals if the mice become autoimmune by raising their autoantibody producing ability caused by the injection of a polyclonal B cell activator (PBA) such as bacterial lipopoly-saccharide (LPS) or dexstran sulfate (col. 8, lines 37-53 and claim 12 in particular). The `198 patent teaches that the glycolipids which contain N-glycolylneuraminic acid including gangliosides with the H-D antigen activity, one of the objects in this invention, are known to exist widely in mouse tissues, so that these glycolipids are autoantigens for mice. Therefore, these glycolipids are thought to have extremely weak immunogenicity. It is very difficult to obtain the monoclonal antibody specific to or against glycolipids containing N-glycolylneuraminic acid according to the conventional methods which use normal mice such as Balb/c mice as immunized animals. On the other hand, it is known that mice with autoimmune disease produce antibodies against autoantigens such as anti-nuclear antibodies or anti-erythrocyte antibodies (see col., 8, last ¶). The `198 patent teaches that the produced antibodies are very effective for study of cancer's occurrence mechanism diagnosis and treatment (see abstract in particular).

The claimed invention differs from the reference teachings only by the recitation that the mouse is Fas function defects and the antigen is glypican in claim 1 such as glypican-3 in claim 6.

Makino et al teach that comparative studies between male BXSB and MRL/lpr mice at the onset period. Makino et al teach that MRL/lpr mice had much higher level of serum IC than male BXSB mice at 13 weeks as assessed by fluid- and solid-phase C1q-binding assays (see abstract).

Lage et al teach that proteoglycans are glycoproteins containing various sulfated glycosaminoglycan residues, e.g., heparan sulfate. These glycoproteins, designated as heparan sulfate proteoglycans (HSPGs), are widely distributed in many tissues, occurring in various forms of extracellular matrices, at cell surfaces, and in intracellular granules. HS is a regulatory polysaccharide. Glypicans, also called glypican-related integral membrane proteoglycans (GRIPS), are one of two major families of transmembrane HSPGs. The glypicans are anchored to membranes by a glycosyl-phosphatidylinositol (GPI) anchor. This covalently attached GPI residue was the source of the term glypican, which is derived from glycosylphosphatidylinositol-anchored proteoglycan (see page 438, under Introduction). Lage et al teach that despite many efforts, no mAb specifically recognizing the GPC3 polypeptide could be generated, it appears obvious that GPC3 is only weakly or not immunogenic in mice.

Claim 7 is included because human GPC3 has 94% sequence identity with the mouse.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make mAb against GPC3 using MRL/lpr mice autoimmune mice. The teachings of Lage et al pertaining to the difficulties in generating mAb specifically recognizing the GP3 polypeptide because GPC3 is only weakly or not immunogenic in mice and the teachings of the `390 publication and `198 patent indicating success in generating specific antibody in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior

art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

The skilled in the art would be motivated to use MRL/lpr mice because MRL/lpr would produce much higher level of serum IC than male BXSB mice.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 02/17/2010, have been fully considered, but have not been found convincing.

Applicant submits that BXSB mice, similarly to the MRL/lpr mouse, exhibits an immunodeficient phenotype as a lupus prone mouse. Applicant concluded that it is unreasonable to judge whether or not the instant claims are unobvious by assessing the capability of MRL/lpr mice to produce antibodies in view of antibody production of BSXB mice. Applicant submits that Makino teaches (i) that there is no difference between the degradation of IC in the glomus between BXSB mice and MRL/lpr mice. Degradation of IC in the glomus is believed to cause lupus glomerulonephritis (LGN), a disease that both BXSB and MRL/lpr mice suffer. Makino further teaches (ii) that the level of IC, which binds to Raji cells, is not different between BXSB mice and MRL/lpr mice. The Examiner notes that BXSB mice and MRL/lpr mice differ in the level of IC binding to Clq and concludes that an ordinary artisan would have believed from this observation that MRL/lpr mice are preferable. However, Applicants submit that the Examiner is using improper hindsight in view of the claimed invention to make this conclusion. As noted above, Makino discloses that there is no difference in IC degradation in the glomus between the mice strains. Further, Makino discloses that the levels of IC binding to Raji cells is not different between the two strains. Accordingly, Applicants submit that an ordinary artisan, reviewing Makino as a whole, would not have come to the Examiner's conclusion that an ordinary artisan would have been motivated to use MRL/lpr mice to achieve the instant invention

However, it remains the Examiner's position that given that the spleen of 13-week-old MRL/Ipr mice contained extraordinary number of IgG-producing cells in spleen as compared with 8-week-old mice or male BXSB mice at 8 or 13 weeks. Further, given that MRL/Ipr mice had much higher level of serum IC than male BXSB mice at 13 weeks as assessed by fluid- and solid-phase Clq-binding assays, would motivate one skilled in the art to choose the MRL/lpr mice in a method for producing an antibody.

Applicant points to Tomer et al., Immunological Investigations, 1988, 17(5):389-424, who teaches that autoimmune antibodies, such as anti-DNA and anti rheumatoid factor antibodies, are immediately generated when a B cell activator, such as LPS, is administered to a normal mouse

(page 398, line 5 to page 399, line 9). Tomer et al further show that a normal mouse, such as Balb/c mouse, activated by LPS and the like, is equally capable of producing autoantibodies as an immune deficient mouse, such as MRL/lpr (page 400, lines 3-24).

It appears that Applicant is admitting that the Blab/c and MRL/lord are interchangeable in a process for producing an antibody at the time the invention was made. Further, Tomer et al uses B cell activator such as LPS, to induce the autoimmune antibodies in the normal Balb/c mice, while the MRL/lpr would produce these autoantibodies without the need for the B cell activator. In the claims there is not requirement to use the B cell activator in the Fas function defects.

Applicant submits that an ordinary artisan would not have recognized from the cited references that a mouse, such as an MRL/lpr mouse, which lacks Fas function, is more preferable than a Balb/c mouse, which is administered LPS and the like, for antibody production against a human antigen, which has a high sequence identity at the amino acid sequence level to a homolog protein over the whole length, of the animal to be immunized. In fact, an ordinary artisan reviewing the cited references would have concluded quite the contrary. In fact, an ordinary artisan reviewing the cited references would have concluded quite the contrary. An ordinary artisan would have recognized that the ability to produce autoantibodies from a mouse with an autoimmune disease would have been similar to a Balb/c mouse, which has been administered LPS or the like. As stated in the previous response, it is Applicants' position that an ordinary artisan would have been reluctant to use a mouse having an autoimmune disease to produce the described antibodies if the ordinary artisan was aware at the time of the invention that there is no advantage to using such a mouse when a Balb/c mouse, modified as described above, may be used. Applicant submits that the cited references teach away from the claimed invention.

It remains the Examiner's position that there is not teaching away in the cited references. Again, it appears that applicant argues that MRL/lpr mouse is equivalent to Balb/c mouse in producing antibodies, i.e., the process in either of the mouse strains is obvious. Further, the claimed process does not require the B cell activation with LPS as required by the normal Balb/c mouse, but not by the MRL/lpr mouse. Moreover, given that the spleen of 13-week-old MRL/Ipr mice contained extraordinary number of IgG-producing cells in spleen as compared with 8-week-old mice or male BXSB mice at 8 or 13 weeks. Further, given that MRL/Ipr mice had much higher level of serum IC than male BXSB mice at 13 weeks as assessed by fluid- and solid-phase Clq-binding assays, would motivate one skilled in the art to choose the MRL/lpr mice in a method for producing an antibody. Accordingly, there is no teaching away in the cited references. The stated advantage of the autoimmune mice is that it produces antibody against less immunogenic glycolipids, which are autoantigens for mice. The `198 patent teaches that it is difficult to obtain monoclonal antibodies specific for glycolipids using conventional methods which use normal mice such as Balc/c mice as immunized animal. On the other hand, it is known that mice with autoimmune disease produce antibodies against autoantigens. Accordingly, there are no teachings away, but rather, the reference provides a clear advantage to use mice with autoimmune disease to produce antibodies against extremely weak immunogenic determinants such as GPC3.

13. Claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-01047390 (IDS ref. No. BB) OR US. Pat. No. 4,965,198 (IDS AA), each in view of Lage et al (2001, IDS CA) and U.S. Pat. No. 5,641,488.

The teachings of the `390 publication and the `198 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the nonhuman animal that develops the autoimmune disease is Fas function defects in claims 1 and 7, the immunogen is glypican protein in claim 1 or a human native protein which has a sequence identity of 94% or more at the amino acid sequence level to a homolog protein of the mouse to be immunized in claim 7 and the mouse is the MRL/lpr mouse in claim 9.

The `488 patent teaches methods for producing an antibody which specifically binds to a chosen antigen using the so-called autoreactive animals, such as mouse strains NZBXSWR(F1) and MRL lpr/lpr (SLE model) animals may be used. "Autoreactive" animals do not require treatment to undergo B cell hypermutation. Such animals need only be immunized with the immunogen of choice when they are in an autoreactive state. Determination of when the animal is in such a state is easily determined by one skilled in the art (see col. 17, lines 23-30).

Lage et al teach that proteoglycans are glycoproteins containing various sulfated glycosaminoglycan residues, e.g., heparan sulfate. These glycoproteins, designated as heparan sulfate proteoglycans (HSPGs), are widely distributed in many tissues, occurring in various forms of extracellular matrices, at cell surfaces, and in intracellular granules. HS is a regulatory polysaccharide. Glypicans, also called glypican-related integral membrane proteoglycans (GRIPS), are one of two major families of transmembrane HSPGs. The glypicans are anchored to membranes by a glycosyl-phosphatidylinositol (GPI) anchor. This covalently attached GPI residue was the source of the term glypican, which is derived from glycosylphosphatidylinositol-anchored proteoglycan (see page 438, under Introduction). Lage et al teach that despite many efforts, no mAb specifically recognizing the GPC3 polypeptide could be generated, it appears obvious that GPC3 is only weakly or not immunogenic in mice.

Claim 7 is included because human GPC3 has 94% sequence identity with the mouse.

The limitations of claims 13 and 14 are inherent to the MRL/lpr mouse.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use MRL lpr/lpr taught by the `488 patent in a method for producing an antibody to GPC3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make mAb against GPC3 using MRL/lpr mice autoimmune mice. The teachings of Lage et al pertaining to the difficulties in generating mAb specifically recognizing the GP3 polypeptide because GPC3 is only weakly or not immunogenic in mice and the teachings of the `390

publication and `198 patent indicating success in generating specific antibody in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such animals need only be immunized with the immunogen of choice when they are in an autoreactive state (i.e., the MRL/lpr mouse need not to be induce with PBA to become autoreactive, spontaneous autoreactive).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 02/17/2010, have been fully considered, but have not been found convincing.

Applicant submits that the cited references teach away from the instant invention. Applicant concluded that the claims are not obvious in view of these references. The `488 is merely cited for teaching MRL/lpr animals. Applicant concluded that the `488 patent does nto remedy the deficiencies of the `390 publication, the `198 publication and Lage.

However, it remains the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make mAb against GPC3 using MRL/lpr mice autoimmune mice. The teachings of Lage et al pertaining to the difficulties in generating mAb specifically recognizing the GP3 polypeptide because GPC3 is only weakly or not immunogenic in mice and the teachings of the `390 publication and `198 patent indicating success in generating specific antibody in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination *In re Sernaker* 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such animals need only be immunized with the immunogen of choice when they

are in an autoreactive state (i.e., the MRL/lpr mouse need not to be induce with PBA to become autoreactive, spontaneous autoreactive).

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 9, 2010

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644